REMARKS

Claims 1-13, 15-29, 32-35,and 41-56 are currently pending. Despite the Applicants' complete rebuttal to this rejection in the last response, which are herein incorporated by reference, the Examiner has nevertheless maintained the enablement rejection.

I. Claims 1-13, 15-29,32-35, and 41-56 are rejected under 35 USC §112, ¶1 as allegedly failing to comply with the enablement requirement.

I. Claims 1-13, 15-29, 32-35, and 41-56 Are Enabled

The Examiner rejects Claims 1-13, 15-29, 32-35, and 41-56 because:

> ... the specification ... does not reasonably provide enablement for a transgenic non-human mammal ...

Office Action pg. 2. The Examiner maintains this rejection from the previous Office Action despite the Applicants providing two Declarations demonstrating that: i) a transgenic goat was created using a parotid secretory protein (PSP) promoter (i.e., BSP30a) that secrets an exogenous protein in saliva; and ii) that the sequences of BSP30a were known at the time of filing of the pending application.

The Examiner has asserted two specific issues in support the pending enablement rejection to which the Applicants disagree for the following reasons.

A. The Specification Adheres To Enablement Requirements By Properly Disclosing Regulatory Elements

As a first issue, the Examiner states that:

> ... the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-lps genes) (p. 27-28) could be used failed to disclose actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva.

Office Action, pp 3-4. The Examiner continues to misstate that the Applicants did not disclose any nucleic acids. As explained in the previous response, patent law encourages that information that is known in the art not be repeated in patent applications, including nucleic acid sequences.

> With respect to a skilled artisan's ability to identify "essential" poxvirus genes ... as of the time of filing ... professional journals had disclosed the DNA sequence of the poxvirus genome along with the locations of the "essential regions". The person of ordinary skill in the art would clearly have possessed such knowledge, and given the ready accessibility of the journals, the absence of incorporation by reference is not problematic. Indeed, "[a] patent need not teach, and preferably omits, what is well known in the art." *Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1534 (Fed. Cir. 1987).*

Faulkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006). Despite this clear direction from the Federal Circuit the Examiner has not accepted the Wheeler Declaration as placing the BSP30a and BSP30b promoters within the knowledge of one having ordinary skill in the art:

> These arguments are not persuasive because the availability of the bovine salivary protein sequence gene and protein as accession numbers in the Gene Bank does not overcome the lack of guidance for specific regulatory sequences that are salivary gland specific cis-acting transcription control region of at least 4.6 kB ...

Office Action, pg 11 – 12. This conclusion by the Examiner is in complete disagreement with the Federal Circuit holdings of *Faulkner*. The existence of the BSP30a and BSP30b sequences as Accession numbers is precisely the type of disclosure *Faulkner* indicates by speaking about "professional journals".

The Applicants respectfully request that the Examiner reconsider the Wheeler Declaration as substantive evidence that the BSP30a promoter sequences was known and available at the time of filing of the Applicants' specification. The level of skill in the art is high enough in the art of transgenic animal development, that given a complete nucleotide sequence of the BSP30a or BSP30b gene, the Applicants' specification provides sufficient guidance to create and use a transgenic animal secreting an exogenous salivary protein. Clearly, the Applicants' specification does satisfy the enablement requirement.

The Examiner again attempts to rely upon the irrelevant teachings within Samuelson arguing that some salivary gland promoters may have limitations;

> This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary glands are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson ...

Office Action, pg 4. The Examiner is apparently ignoring the fact that the Applicants clearly rebutted this rejection basis in the last office action because Samuelson does not relate to the PSPs as taught by the Applicants:

> Smaller Psp transgenes containing varying amounts of 5'-flanking sequence fused to a Psp minigene were also expressed in the salivary gland; however, the level of expression in the parotid gland was only 1% of the endogenous gene levels (56)[1]. ... Analysis of various 5' deletion constructs of the Psp minigene localized the position of critical transcriptional control sequences for basal expression in both parotid and SLG to a region between –4.6 kb and –3.1 kb. These results indicate that the minimal salivary-specific enhancer(s) are within 5 kb of the gene and that enhancer(s) for high level expression in the parotid are located elsewhere within the 25-kb cosmid clone.

Samuelson, pg 217 (emphasis added). Clearly, those skilled in the art recognized the limitation at the time and found the answer to eliminate the problem. Thus, based upon reading Samuelson, one having ordinary skill in the art would not be motivated to repeat Mikkelsen's minigene experiment using a Lama minigene and expect high level expression. Certainly, the Applicants did not. The Applicants' specification contemplate using secretory promoters having 5' flanking regions that are 4.6 kB or larger. *See, Applicants' Specification pg 27 ln 15-16.* Despite this enabling disclosure, the Examiner now argues that the claim is too open ended:

> ... simply contemplating that using promoters that are 4.6 kB or larger does not provide any guidance for any boundaries for designing the claimed salivary gland-specific transcription control region of at least 4.6 kB. An artisan will not be able to design specific salivary gland 5' flanking DNA required for salivary gland specific expression without set sequence boundaries.

Office Action, pg 8. In contrast to the Examiner's belief, the ranges of the 5' flanking regions of secretory promoters were established and disclosed in the Applicants' specification in US Patent No. 6,140,552 To Deboer et al. entitled "Production of recombinant polypeptides by bovine species and transgenic methods" that was incorporated by reference (*See, Applicants' Specification pg 75 ln 16*):

> The amount of distal 5' expression regulation sequence depends upon the endogenous gene from which the expression regulation sequences are derived. In general, however, such sequences comprise 5' flanking regions of approximately 1 kb, more preferably 16 kb and most preferably about 30 kb of 5' flanking sequence. The determination of the

[1] Mikkelsen et al., Nucl Acid Res. 20:2249-2255 (1992), and discussed within Applicants' specification.

> optimal amount of distal 5' expression regulation sequence used from any particular endogenous gene is readily determined by varying the amount of distal 5' expression regulation sequence to obtain maximal expression. In general, the distal 5' expression regulation sequence will not be so large as to extend into an adjacent gene and will not include DNA sequences which adversely effect the level of transgene expression.

'552 patent, col 9 ln 53 - 59 [emphasis added]. DeBoer et al. clearly states that finding an optimal 5' flanking sequence of a secretory promoter is within the abilities of one having ordinary skill in the art (see, underlined portion). Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have clarified Claims 1, 20, 29, 41, and 52 by an amendment to identify the upper range of the 5' flanking region as "30 kb", as enabled by the '522 patent. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application. Further, the secretory promoters disclosed in '522 patent are capable of secreting transgenic proteins in saliva:

> Transgenesis may also by detected by assaying for expression of the recombinant polypeptide in a tissue, secretion (e.g., saliva), or other body fluid. In the case where the goal is expression of a recombinant polypeptide in milk of cows it will be especially useful to assay the saliva of bulls for expression levels. This is because some mammary specific promoters may also cause salivary gland expression, albeit at low levels. *See, e.g., Archibald et al. (1990) Proc. Nat. Acad. Sci. USA 87Z:5178-5182.*

'522 patent, col 19 ln 19-27. In fact, the '522 patent discloses a promoter construct that results in creation of a transgenic cow producing transgenic protein in saliva. *See, Example 26.*

The Applicants submit that the Applicants' specification does enable the pending claims. The Examiner is respectfully requested to withdraw the present rejection.

B. The Specification Meets Enablement Requirements By Properly Disclosing The Creation Of A Transgenic Animal

As a second issue, the Examiner states:

> ... the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. *The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva.* However, the working examples failed to disclose which saliva regulatory elements were used in the creation of the transgenic cows.

Office Action, pg 6. The Applicants point out that the Examiner has merely rephrased the first presented issue, for which the Applicants provided rebuttal evidence in Section A above. Here, the Examiner admits that the Applicants have presented a working example of creating a transgenic cow (italicized portion), but discounts the example based upon the improper conclusion that the Applicants did not disclose any regulatory elements (underlined portion). The Examiner is reminded that this working example does provide adequate guidance because the specification is supported by US Patent No. 6,140,552 that is explicitly incorporated by reference.

> Bovine embryo's are obtained and injected much as described above for mice and pigs, in accordance with the procedures for cows described in US patent number 6,140,552 which is incorporated by reference particularly in parts pertinent to microinjection of DNAs and other methods to produce transgenic bovine animals.

Applicants' Specification pg 75 ln 14-18 [emphasis added]. Consequently, the Applicants submit that the Examiner has misapplied the holdings of *Genentech v. Novo Nordisk* for the proposition that:

> If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art.

Office Action pg 6 [emphasis added]. The Applicants' specification provide specific Examples teaching the "conditions" under which the creation of a transgenic animal can be carried out. The guidance for the "starting materials" are evidenced by the Wheeler Declaration and the teachings within the '552 patent.

Further, the Applicants have created a transgenic goat, as evidenced in the Erickson Declaration, based upon guidance provided in the Applicants' specification:

> ... expression control regions from the gene for parotid secretory proteins ("PSP") generally are suitable to engineer salivary-gland specific gene expression, in the manner Mikkelsen and so-workers used control regions from the gene for mouse PSP ("moPSP") to engender parotid-specific transgenic expression in mice.
>
> [...]
>
> Accordingly, the PSP paradigm for salivary gland-specific expression in mice can be followed to isolate the genetic elements for efficient, salivary gland-specific expression in other animals.

Applicants Specification, pg 27 ln 7-26. In accordance with this guidance, the Examiner has acknowledged that the Applicants have successfully created a transgenic goat using a PSP promoter (i.e., for example, by using a BSP30a promoter):

> ... the Erickson Declaration describes the expression of both BSP30a and BSP30B ... [in] ... salivary gland tissue.

Office Action pg 10. Consequently, the Applicants respectfully request the Examiner to withdraw the present rejection.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 781-828-9870.

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By: _____

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